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DESCRIPTION OF CASES OF SHELL SHOCK

MYERS, C.S.

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L S HEARNshaw A SHORT HIST. OF BR. PSYCH

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injection of the guinea-pig with anti-rabbit-plate serum, and *vice versa*. Recently, being in possession of a supply of anti-guinea-pig-plate, anti-rabbit-plate, and anti-rat-plate sera, one of us has carried out the following experiment, which shows clearly that a heterologous anti-plate serum has no purpura-producing property.

TABLE V.

Rat A, 150 gm., received 7/12/1914,	3 c.c. anti-rat-plate serum.
" B, 90 " " " "	3 " anti-guinea-pig-plate serum.
" C, 140 " " " "	4 " anti-rabbit-plate serum.
(All inoculated subcutaneously.)	
Guinea-pig A, 230 gm., received 7/12/1914,	3 c.c. anti-guinea-pig-plate serum.
" B, 230 " " " "	3 " anti-rat-plate serum.
" C, 230 " " " "	4 " anti-rabbit-plate serum.
(All inoculated subcutaneously.)	
Rabbit A, 400 gm., received 7/12/1914,	4 c.c. anti-rabbit-plate serum.
" B, 380 " " " "	4 " anti-guinea-pig-plate serum.
" C, 380 " " " "	4 " anti-rat-plate serum.
(All inoculated intraperitoneally.)	

On Dec. 8th Rat A showed several purpuric spots near tail and also on legs. Other two rats showed nothing and appeared quite lively. Guinea-pig A had an extensive hæmorrhagic infiltrate over the whole of the abdomen and did not appear well. The other two animals showed no purpura and were quite lively. Rabbit A had numerous purpuric spots all over its skin and was obviously ill. The other rabbits were quite lively and showed no purpura. On Dec. 9th the animals inoculated with the homologous sera were still more drowsy and listless. Other animals appeared quite well. On Dec. 10th Guinea-pig A and Rabbit A dead.

Post mortem: Guinea-pig A showed beautiful skin purpura, extensive oedematous and hæmorrhagic infiltrate spreading over abdomen from seat of injection and extending deeply into the thigh muscles, and miliary purpura of stomach. There was no cataract, and the urine was quite clear. Rabbit A showed a large oedematous and hæmorrhagic subcutaneous area over upper thorax, neck, and fore limbs, also a larger hæmorrhage under skin of left cheek. Miliary purpura of stomach and slight purpura of intestine. Liver yellow and mottled. No cataract. Urine quite clear.

The other animals remained well and put on weight. Dec. 11th: Rat A dead. Post mortem: Purpura of skin particularly marked over skull and cheek. A few spots in pyloric portion of stomach and a few in small intestine. Urine was blood-stained (hæmoglobinuria).

The other animals, which received the heterologous plate sera, remained well and put on weight.

#### Summary and Conclusions.

1. Data have been recorded on the blood changes in guinea-pigs after inoculation with anti-guinea-pig-plate serum. The early fall in the number of platelets simultaneously with the outburst of skin purpura is found to be a marked feature.

2. Purpura has also been produced in rabbits and rats by inoculation with the respective anti-plate serum. The blood changes in rabbits have been followed with results similar to those obtained in guinea-pigs.

3. Anti-plate serum, in addition to its purpura-producing properties, possesses in common with other cytolytic sera considerable lytic powers, which in all probability contribute largely towards the fatal issue in small animals. Death, however, may occur as the result of extensive hæmorrhages alone without any obvious lytic changes as evidenced by hæmoglobinuria.

4. Sera obtained by immunisation with red cells or leucocytes do not produce purpura.

5. Purpura is not produced by inoculating animals with heterologous anti-plate sera.

The histology of the purpuric lesions will form the subject of a later communication.

## A CONTRIBUTION TO THE STUDY OF SHELL SHOCK.

BEING AN ACCOUNT OF THREE CASES OF LOSS OF MEMORY, VISION, SMELL, AND TASTE, ADMITTED INTO THE DUCHESS OF WESTMINSTER'S WAR HOSPITAL, LE TOUQUET.

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THE remarkably close similarity of the three cases which are described in this paper is shown in the following synopsis:—

	Case 1.	Case 2.	Case 3.
Cause...	Shells bursting about him when hooked by barbed wire.	Shell blowing trench in.	Shell blew him off a wall.
Preceding period of sleeplessness.	As in Case 1.	As in Case 1.	?
Vision ...	Amblyopia. Reduced visual fields.	"	As in Case 1.
Hearing ...	Slightly affected for a brief time.	Not affected.	As in Case 2.
Smell ...	Reduced acuity.	Total anosmia.	Unilateral anosmia and parosmia.
Taste ...	Almost absent.	Reduced acuity.	As in Case 2.
Other sensations ...	Not affected.	As in Case 1.	As in Case 1.
Volitional movements	"	"	"
Defecation	Bowels not opened for five days following shock.	"	"
Micturition	Urine not passed for 48 hours.	Not affected.	As in Case 2.
Memory ...	Apparently slightly affected.	Very distinct amnesia.	"
Result of treatment	Gradual improvement by rest and suggestion.	As in Case 1, supplemented by hypnosis	As in Case 1.

CASE 1.—Private, aged 20. Admitted on Nov. 5th, 1914. On the nights of Oct. 28th and 29th he slept in the booking hall of X station; "not much sleep there." On the 30th he motored in a bus from X to Y, arriving there at 7.30 P.M.; billets found at 8 P.M.; on guard from 10–11.30 P.M., and from 1.45–3.45 A.M. At 11 A.M. on the 31st for the first time he went to the firing line. His platoon advanced to one set of trenches and then crossed the road to another, only to find it filled with cavalry and to be told that there was no room for them. During the retirement from this trench, at 1.30 P.M., they were "found" by the German artillery. Up to that time he had not been feeling afraid; he had "rather been enjoying it," and was in the best of spirits until the shells burst about him.

He was now retiring over open ground, kneeling on both knees and trying to creep under wire entanglements, when two or three shells burst near him. As he was struggling to disentangle himself from the wire three more shells burst behind and one in front of him. (An eye-witness in this hospital says that his escape was a sheer miracle.) After the shells had burst he succeeded in getting back under the wire entanglements; all his comrades had retired already. He managed to get into a trench, and as the firing slackened he rejoined his company. Immediately after the shell had burst in front of him his sight became blurred. It hurt him to open his eyes, and they "burned" when closed. The right eye seemed to have "caught it" more than the left. At the same moment he was seized with shivering, and cold sweat broke out especially round the loins. He thinks the shell behind him gave him the greater shock—"like a punch on the head, without any pain after it." The shell in front cut his haversack clean away and bruised his side, and apparently it burned his little finger. It was this shell, he says, which "caused his blindness."

Falling in with two comrades, he was led by them, one on either side, to the dressing station. He opened his eyes occasionally to see where he was going, but everything

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CAPT. C. S. MYERS, R.A.M.C.: THE STUDY OF SHELL SHOCK.

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appeared blurred except at the first moment of opening. There was no doubling of objects; they seemed to "dissolve." He was crying the whole time and worrying as to whether he was going blind. He kept turning over in his mind the succession of events from the beginning of the advance to the bursting of the shells. At the dressing station he was still crying and shivering; he was taken thence to a hospital by horse ambulance, where he was given brandy, and then sent on by horse ambulance to another hospital, and thence by motor ambulance at night to X, where he arrived early on Nov. 1st. He thinks he must have slept on the ambulances, as he remembers nothing.

From Nov. 1st to 4th at X; his eyes were bandaged and drops were instilled which "burnt terribly." No numbness or anaesthesia observed. Slight deafness, which soon passed off. On Nov. 1st he shivered in bed almost incessantly; his thoughts were still running on events between the advance and the bursting of the shells. No shivering after Nov. 3rd. He says he did not micturate from Oct. 30th P.M. until Nov. 2nd P.M., and did not defaecate from Oct. 30th until Nov. 5th (after aperient here). No involuntary passage of urine or faeces.

Past history.—He had been for two months in the Aisne district on the lines of communication, sleeping badly all that time owing to lumbar pains (and toothache during the first three weeks). He had failed to pass a medical examination some time previously because of renal trouble (abnormal amount of albumin in water) until after a long period of treatment. He had had lumbar pains a few nights before coming to France.

Present condition.—Nov. 6th.—A well-nourished man of nervous temperament, flushed complexion, and dark eyes. Movements normal; skin sensations normal. Eyes, fundi normal. Fields distinctly contracted, especially on temporal sides. Right eye—can read at normal distance, but "things have a slight haze round them." Left eye—the haze is much greater; is unable to see letters until they are quite near.

Nov. 7th.—Says he has lost his sense of taste and smell since the shells burst round him. Gets up now.

Nov. 9th.—Woke up last night and found himself crying, "not thinking of anything in particular"; he at once "pulled himself together."

Nov. 10th.—Tested for taste (tongue protruded) and smell in order mentioned:—

- |                                   |   |
|-----------------------------------|---|
| (1) Very strong sol. of sugar ... | Slightly sweet (only tasted after the tongue had been moved about). |
| (3) " " " salt ...                | No taste.   |
| (4) " " " acid ...                | No taste, but "a peculiar feeling as if it dried the tongue."       |
| (7) " " " quinine...              | No taste (later, "a peculiar feeling of biting on the tongue").     |
| (5) Carbolic acid (1:40) ...      | No smell.   |
| (6) Ether ...                     | Faint smell, like collodion.  |
| (8) Peppermint (strong) ...       | Faint smell of peppermint.  |
| (2) Tincture of iodine ...        | No smell.   |

Hypnosis tried; patient explains later—"I insisted on resisting." Suggestions offered during concentration. Nov. 15th.—Says his taste and smell are returning. Fields of vision still restricted, perhaps slightly less so. Nov. 15th.—He was transferred to England for further treatment.

On Nov. 16th the patient was admitted to the Middlesex Hospital, London, under the care of Mr. Arnold Lawson, who has kindly allowed me to append his note of the condition of the patient's eyes:—

Nov. 25th: R. E. —	+1.75	L. E. —	-1
	+2.25		+2

Visual acuity, each eye 6/36; when under correction 6/18. Just below and to the outer of the left disc is a small clear buff patch in the choroid. The upper inner margins of the discs are somewhat blurred and more densely white than elsewhere. These features are probably not pathological. The fields are definitely restricted, especially on the nasal side of the retina, being limited here to 40° in the right eye and to 70° in the left. No central scotoma. Taste and smell were found affected on admission, but these recovered earlier.

Nov. 27th.—General condition improved. Not so "nervy." Visual acuity under correction, R.E. 6/24, L.E. 6/18. The patient is now (Feb. 1st) attending the hospital as an out-patient.

CASE 2.—Corporal, aged 25. Admitted on Dec. 11th, 1914. The patient says that he was buried for 18 hours on Dec. 8th owing to a shell bursting and "blowing in" the trench in which he lay. Can remember nothing until he found himself in a dressing station at a barn lying on straw. He says that then he could not see and that for this reason he fell over something when he got up and walked about there. As to his past history, he came out to the war on August 13th, and was in the last two days' retreat at Mons and after at La Bassée. Has slept very badly since the start, often when billeted taking large doses of whisky to procure sleep. Has led a "fast" life and has had recent domestic worry.

Present condition.—Dec. 12th.—A healthy-looking man with flushed face and large dark eyes with wide pupils. His general manner does not inspire one with confidence in his reliability. Complaints of pains in abdomen, back and limbs, and of difficulty in seeing. The pains are chiefly in the knees and ankles. His sight has been very indistinct since he was "buried." Says that if he looks at an electric light it takes him "five minutes" before he can see anything again. His vision has much improved since Dec. 8th, but he can only read when the type is close to his eyes and not for long; "it all becomes blurred." Heart, lungs, and joints appear normal. Abdomen distended and tender in lower part. Bowels not opened for five days. Aperient is effective. Vision: R.E. 5/60, L.E. 2/60. Media clear. Fundi natural. Pupils and eye movements normal. Hearing normal.

Dec. 17th.—Smell: Fails to smell peppermint, ether, iodine tincture, and carbolic acid (1:40). Taste (tongue protruded): Very strong solution of sugar—tasted only after movements of tongue are allowed. Very strong solution of salt—"feels like petrol does on the hand," tasted only after movements of the tongue are allowed. Solution of acid—"salty, like alum."

Dec. 19th.—Complains that he does not sleep, but the sister in charge of his ward says that he sleeps well. Treatment by suggestion (during and without hypnosis) was begun, and continued daily until patient's transfer to England. On the second trial and afterwards a state of light hypnosis was easily induced. The deeper stages, involving hallucinations, anaesthesia, and post-hypnotic amnesia, could not be reached on any occasion. But the lighter stages (in which the patient responded to suggestions that he could not open his eyes, close his hand, stop laughing, and the like) sufficed to bring about assurance of a good night's sleep, gradual restoration of memory, and (later) improvement in visual and olfactory acuity, in near vision, in visual fields, and in colour sensibility. The improvement in visual acuity and near vision is shown in the following table:—

	Visual acuity. Both eyes.	Near vision.	
		Right eye.	Left eye.
Dec. 15th.	Before hypnosis, 5/60.	No. 15 Jaeger (badly).	Less than No. 15 Jaeger.
" 23rd.	After " 3/36.	No. 12 Jaeger	No. 15 Jaeger (badly).
" 26th.	Before " 1/6.	No. 6 "	No. 12 Jaeger
	After " —	No. 4 "	No. 10 "
" 27th.	" " 2/6.	No. 2 "	No. 10 "
" 28th.	No " 4/6.	No. 1 "	No. 4 "

<sup>1</sup> Colonel W. T. Lister, A.M.S., reports (Dec. 15th) that under homatropine and cocaine the refraction of the patient's eyes is as follows:

R.E. —	+2.5	L.E. —	-1?
	+2.5		0 or -0.5

He makes at the same time the following note on the fundi: "Right eye: Sector below disc is deficient in retinal pigment, so that the choroidal vessels are abnormally visible, but there is no pathological pigmentation and there are no areas of atrophy. Left eye: Internal crescent; vessels drawn to nasal side; and lack of retinal pigment on nasal side (nasal staphyloma). The atrophic appearance is more marked in this eye; even the choroidal pigment is deficient, giving a pale area. Maculae normal. Both discs are pale, and there is connective tissue by the sides of the vessels. The whole condition, in my opinion, might be congenital."

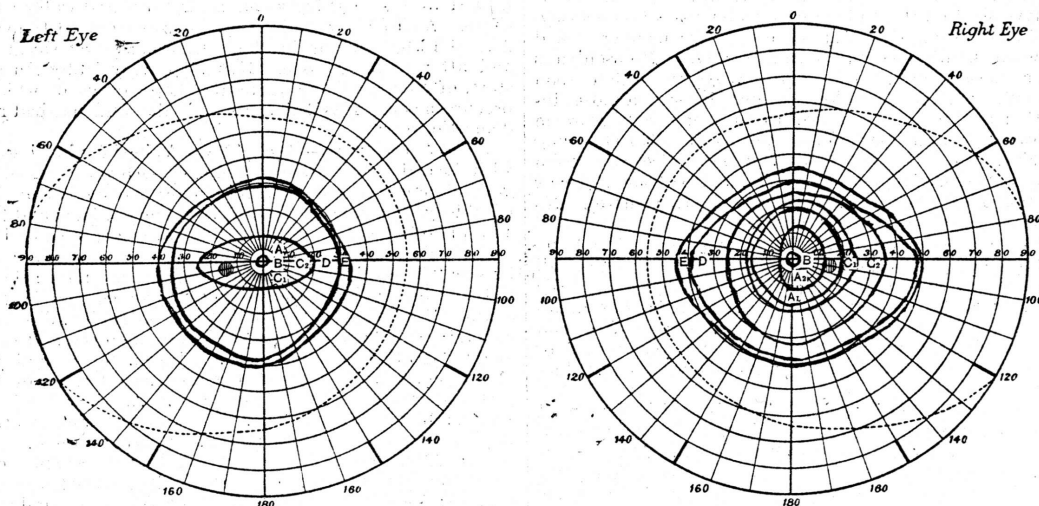
The improvement in visual fields is shown on the annexed Chart 1.<sup>2</sup> The "functional" character of this restriction of fields is shown by the fact that the patient was never observed to collide with objects when walking, and that he was able to box here when convalescent.

The improvement in colour sensibility was as follows:—  
Dec. 14th: Half-inch square of colour recognised at 22 cm. R.E., 7.5 cm. L.E. Dec. 27th: 350 cm. R.E., 50 cm. L.E.  
The sensibility of the eyes to red appeared to be keener than

a bit when they got me out. I got up and then fell down, and it was all a 'wash out.'

Under hypnosis he confirms the above, adding that in his struggles in the trench he "said a prayer or two," and that when he fell asleep he thought himself in the R. Hotel at S., where he had lived for years and is well known. "I was listening to a young lady I know [not intimately] playing the piano. I saw Mr. S. [the landlord] and Mrs. S. The sleep and dreams kept coming and going. It was

CHART 1.



Perimeter charts from Case 2. A, Dec. 14th; A<sub>1</sub> at start, A<sub>2</sub> after testing other eye; B, Dec. 21st; C, Dec. 26th, C<sub>1</sub> before hypnosis, C<sub>2</sub> after hypnotic suggestion; D, Dec. 27th; E, Dec. 28th.

that to any other colour. Thus the red square was recognised at 100 cm. by the left eye on Dec. 27th, while other colours (yellow, blue, and green) could only be recognised at 50 cm. So, too, on Dec. 14th the visual field for the recognition of coloured squares was limited in both eyes to the fovea save in the case of red, the field for which in the right eye extended definitely, though slightly, beyond the fovea towards the nasal side of the retina.

The improvement in olfactory acuity is shown by the fact that on Dec. 27th he was able to smell and to recognise ether, peppermint, camphor, and turpentine, although still unable to smell carbolic acid (1:10), tincture of iodine, or methylated spirit.

The gradual restoration of memory occurred as follows:—  
Dec. 22nd.—During hypnosis suggestions made evoked a description of how the ground fell in on him at the trenches. He says that he was buried up to the neck and that Sergeant L. dug him out. Men of the N. Regiment (not of his own regiment) took him to their dressing station, but the medical officer there "packed him off" to the dressing station of the M. (his own) Regiment. He can now remember Captain S. (attached to his regiment from the —) speaking to him and giving him a drink. He spoke to him when he reached the barn (the M.'s dressing station). While under hypnosis the patient is told that he will remember this when he awakes. He does so, but cannot explain why he had not been able to recall it before.

Dec. 23rd.—To-day, before hypnosis, he remembers another "big hospital" to which he was taken on leaving the barn—a "big square room with a stove in the centre"—opposite which he was placed. But he cannot recall how he got there, or how he left to come here by train. He cannot remember being carried on a stretcher until they took him out of the train at Étaples (the railway station for this hospital). He says that there was "no light" in the barn all the time he was there (24 hours). He remembers struggling in the trench "for hours" after he was buried. Finally he gave it up. "I went to sleep, and was enjoying myself at home when they started 'messing me about.' Someone fell on me and woke me up. I 'tumbled to things

dark when they dug me out. After I got out a chap said 'the fellow's mad,' and I said 'You're a liar.' ..... Now, I remember a place between the barn and the hospital, rather a smart building, a long, low place. I was on a stretcher there. I must have got there by a horse ambulance, but I cannot remember this."

Dec. 26th.—Before hypnosis he recalls going to the clearing hospital (just mentioned) from the barn in a horse ambulance on a stretcher at midnight. He says: "I can remember talking to a major the next morning and having a sleeping draught at night. Then I went to another hospital at B. I had a ride in a motor ambulance on a stretcher, but whether this was from or to that hospital I cannot remember. I remember the journey in the train here distinctly. There were continual offers of tea, cocoa, sweets, and cigarettes. They wouldn't let us sleep for these things. I had a bad headache all the way down from the trenches. I did not bother much about my sight, as I thought it was imaginary. It wasn't until I got rid of the pain in my stomach which I came in with that I began to find my sight wouldn't let me read."

Dec. 27th.—While in hypnosis he gives the name of the man in the same trench with him as K. He "sees" very clearly the position of the trenches, their shallowness and covering. He remembers that he had been two days in the reserve trenches before he was sent on Dec. 7th to the firing line. He says, "The explosion lifted us up and dropped us again. It seemed as if the ground underneath had been taken away. I was lying on my side, resting on my hand, when the shell came. I got my right hand loose, but my left was fixed behind a piece of fallen timber. At last I dropped off to sleep and had funny dreams of things at home. One dream in particular I have thought over many times since. I haven't been able to make out why I should dream of the young lady playing the piano. I don't know her name and don't think I have seen her above twice."

Dec. 29th.—Before hypnosis he says that he can now "see" the N.'s dressing station—a one-storeyed house with two non-communicating rooms. He was taken first into the left-hand room, and later into the other in which the medical officer sat. No further information obtainable under hypnosis. He cannot recall how he got to the N. dressing station from the trenches.

<sup>2</sup> My thanks are due to Colonel Lister, A.M.S., who, by presenting the hospital with a portable perimeter and test types, made these observations now possible.

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To recover the memory of this period other methods, in addition to hypnosis, were vainly tried. His dreams were generally of incidents belonging to earlier periods of the war, never of the trench-shelling. Attempts to obtain revival of the lost memories by getting him (a) to concentrate his attention on the scene of the shell bursting or of the N. dressing station, or (b) to record his thoughts when in a state of reverie, were fruitless.

How far the patient's memory, so far as it returned, can be trusted is not altogether certain. A man of the same regiment happened to be wounded here at the time. He believes that the patient could not have remained in the trench for longer than an hour after the shell had burst. He declares that he saw him get out of the trench and report himself sick to Corporal R., and that he heard Corporal R. tell the patient to go off on foot to the M. dressing station. Until the day after the patient's arrival at the barn he never saw the patient again, when he was brought in himself there. He says that the doctors at the barn considered the patient "off his head." He does not believe that the N. Regiment was anywhere in the neighbourhood. He says that the man K. had been mortally hit some days before.

On further examination the patient says he has no recollection of reporting himself to Corporal R. or of meeting his fellow patient while at the barn, and he is quite certain that *somehow* he reached the N.'s dressing station before he got to his own.

On the other hand, another fellow patient here happened to belong to the N. Regiment and was able to confirm the patient's account by stating that the trenches of the N. Regiment were on that day

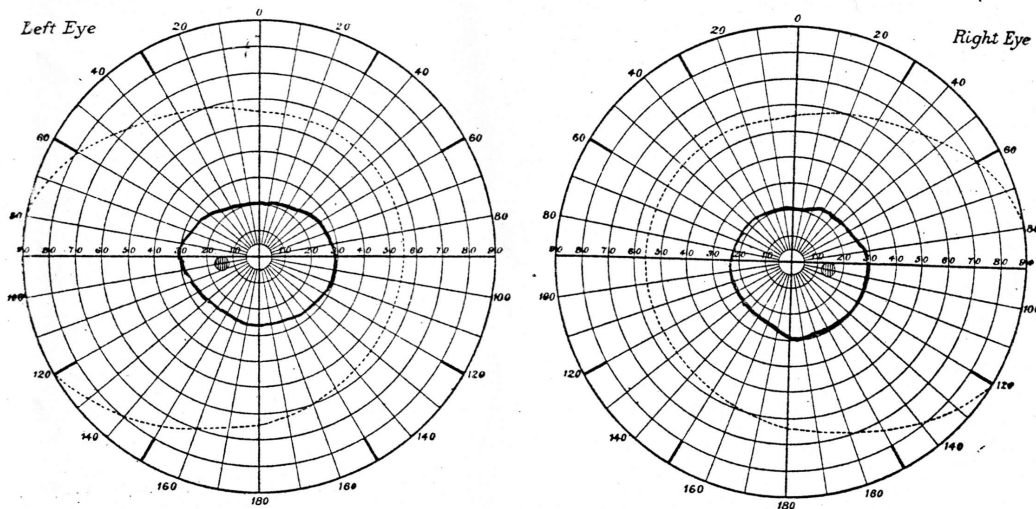
and was then brought, as he avers, to the dressing station by men of the N. Regiment. But of this last point the patient is not now so certain. He still insists that a man stepped into his fallen trench on top of him.

On Dec. 30th the patient was transferred to England for further treatment, and on the 31st he was admitted to the London Temperance Hospital under the care of Mr. J. S. Hosford, whence he has, I understand, now been discharged.

CASE 3.—Private, aged 23. Admitted on Jan. 26th, 1915. The patient says that he was blown off a heap of bricks 15 feet high owing to a shell bursting close to him. Thinks he must have fallen into a pool of water, as he next remembers finding himself, about 3 P.M. the same afternoon, in a cellar near a church with his clothes drenched. He does not know how he got there or how he left the cellar, but he remembers being in another hospital before he was admitted here. He cannot say if anyone was in the cellar with him. He remembers someone in the train talking to him and reminding him of being in the cellar.

*Present condition.*—Jan. 27th.—A healthy-looking man, well-nourished, but obviously in an extremely nervous condition. He complains that the slightest noise makes him start. His legs feel weak, and he has pain in the precordial region. His *sight has been very much impaired* since the shock. Distant vision, he says, is affected, and objects and type become blurred when long looked at. He has slept very little the last two nights. Heart, lungs, and joints appear normal. Abdomen, general spasm of muscles of wall on being touched. Hands tremulous. Knee-jerks normal, but the first attempts to evoke them provoked a spasm of the calf muscles and a few general convulsive movements as the patient lay in bed. His hands became very tremulous and his forehead sweated profusely. He appeared as if about to faint, and says that he felt cold and dizzy, and experienced "round and round movements of the stomach." The slightest touch on the

CHART 2.



Perimeter charts from Case 3, showing contraction of fields.

immediately next to those of the M. Regiment, and that the N. and M. dressing stations were situated in the same village, the former in a cottage about three-quarters of a mile beyond the latter, so that one would have to pass the M. dressing station on the way from the trenches to the N. dressing station.

There is hence a possibility that the patient wandered in a state of somnambulism from the trench past his own dressing station to that of the N.'s or that he wandered first into the N. trenches

legs provoked well-marked spasm of the quadriceps muscles of the same thigh. Plantar reflexes not obtainable. Extensor muscles of the toes appeared to be in a state of tonic contraction.

Jan. 30th.—Slept well last night for the first time. *Bowels not opened for five days* since the shock. Took an aperient last night and this morning; bowels open to-day. *Eyes:* Fundi normal. *Fields, distinctly contracted*, as in Chart 2. Near vision, either eye, No. 14 Jaeger; less for short words. Visual acuity (investigated by Colonel Lister, A.M.S.)—at first 6/24, but improved by encouragement and the indiscriminate use of weak + or — lenses to nearly 6/6.

*Smell:* Has complained until to-day of a subjective sensation of the odour of cordite. This has left him "since the bowels were open." *Left nostril fails to detect* smell of ether, peppermint, eucalyptus, ammonia, carbolic acid, or iodine tincture, all of which, save the last, are at once recognised when placed beneath the right nostril. No signs of nasal obstruction. *Taste:* Only tastes very strong solutions of sugar, salt, and acid, and then only when the tongue has been withdrawn and moved about the mouth; the taste is described as "faint."

*Feb. 1st.*—He complains that he gets very excited when anyone addresses him. He still fails to remember how he got to the cellar, but he now remembers someone there asking him his name and regiment. He says: "When I got into the hospital before I came to this one I can now remember being put against a wall and then being taken into a small room to see the doctor, who gave me a ticket and told me I was suffering from concussion. I think I must have gone to sleep after this, as I don't remember anything else until I was in the train. There a Royal Army Medical Corps bearer brought me a German prisoner to talk to. He was in the Bavarian Guard and had just seen his first action."

[Patient is still under treatment.]

Comment on these cases seems superfluous. They appear to constitute a definite class among others arising from the effects of shell-shock. The shells in question appear to have burst with considerable noise, scattering much dust, but this was not attended by the production of odour. It is therefore difficult to understand why hearing should be (practically) unaffected, and the dissociated "complex" be confined to the senses of sight, smell, and taste (and to memory). The close relation of these cases to those of "hysteria" appears fairly certain.

I have to thank Captain W. P. S. Branson and Captain H. Pritchard, R.A.M.C., in whose wards these patients were placed, for permission to make these investigations, and Major Gordon Watson, R.A.M.C., Commandant, for permission to publish them.

## THE PSEUDO-LÆVULOSE OF DIABETIC AND OTHER URINES.

By P. J. CAMMIDGE, M.D. LOND.,

AND

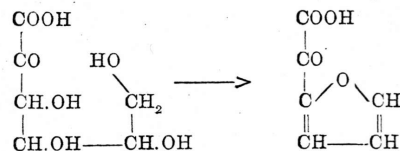
H. A. H. HOWARD, B.Sc.

In a previous paper<sup>1</sup> we pointed out that the lævulose usually met with in urine, unlike the lævorotatory sugar of plant origin, is precipitated from acid solutions by basic lead acetate, resembling in this respect glucuronic acid. This observation appears to have been first made by Külz, who published in 1890 a paper<sup>2</sup> giving the result of his analyses of the so-called urinary lævulose. Like plant lævulose, this substance reduces copper and bismuth in alkaline solutions, is lævorotatory, and is fermented with brewer's yeast. Külz also found that with phenylhydrazine it gave an osazone which in appearance, melting point (205° C.), and on analysis corresponded to dextrosazone. According to his analysis it has a formula  $\alpha\text{CH}_2\text{O}$ . Unlike plant lævulose, however, it could not be obtained in a crystalline form, but was only secured as a syrup. The rate at which it reduced copper solutions, its rapidity of fermentation, and its specific rotatory power, but above all the ease with which it was precipitated by hydrates of the heavy metals, further suggested that urinary

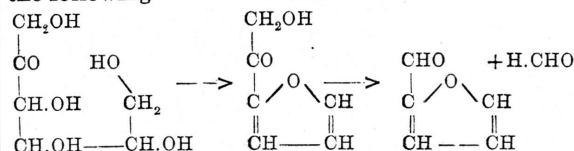
and plant lævulose were not identical substances. Other workers have since published similar results, but no attempt appears to have been made to establish the exact nature of the substance.

In diagnosing lævulosuria reliance has been placed upon a generally positive reaction with Seliwanow's test and the different readings obtained by reduction and the polarimeter. Borchardt, using a modification of Seliwanow's test, has claimed that lævulose does not occur in the urine, and that previous statements to the contrary were due to want of care in testing for it. In his modification the urine is treated with hydrochloric acid and resorcin, made alkaline with sodium carbonate, and then extracted with ethyl acetate. On carrying out this test with a solution of plant lævulose the ethyl acetate extract is coloured red, but with urines giving the ordinary Seliwanow reaction the watery solution retains the pigment and the extract is yellow.

These results obtained with Borchardt's test would be explained if, instead of lævulose, an acid with the constitution,  $\text{CH}_2\text{OH}(\text{CH.OH})_3\text{CO.COOH}$  were present. The reaction would then be—



—and this derivative being a ketonic acid would dissolve in the sodium carbonate solution and not be extracted by the subsequent treatment with ethyl acetate. If, however, lævulose were present the following reactions would occur:—



—and the furfuryl derivative being non-acid in character would not be soluble in the sodium carbonate solution, and hence would be extracted by the ethyl acetate. Since the unmodified Seliwanow and Pinow reactions are readily obtained in a considerable number of cases, and in view of Borchardt's claim that true lævulose never occurs in the urine when tested for by his method, it seemed to us that the so-called lævulose might be the hitherto undescribed ketonic acid, of which we have just given the formula. This formula would explain its resemblance to glucuronic acid with respect to lead acetate, and would also admit of the formation of an insoluble calcium salt and a characteristic methylphenylhydrazine derivative.

In order to investigate these points and to establish the identity of the substance specimens were prepared by the following procedure:—

The urine was concentrated to a fifth of its volume and a saturated solution of lead acetate added, using one-tenth of the original volume of urine taken. The mixture was then heated on a water bath at 90° C., cooled, filtered, and the precipitate washed with water. The precipitate was suspended in 100 c.c. of a saturated solution of sodium sulphate and digested for two hours, when it was diluted to 500 c.c., filtered, and the filtrate tested for lead. When all the lead was found to have been removed the filtrate was mixed with 50 c.c. of saturated calcium chloride solution and 50 c.c. of lime water. After standing for two hours the precipitate that had formed was filtered off, well washed

with water, content of the 6 cases with (ii.) 9.5 per cent. (v.) 9.4 per cent. calcium content (C<sub>6</sub>H<sub>8</sub>O<sub>7</sub>)<sub>2</sub> Ca.

To separate suspended in passed through precipitate concentrated by thick, yellow separated, even a sweetish brewer's yeast and bismuth.

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10 c.c. of described with 20 grm on a water cooled and carbonate filtered. filtered, co absolute alc was filtered alcohol, 0.7428 grm sulphate, original of experim cent. of

<sup>1</sup> THE LANCET, Sept. 26th, 1914, p. 791.

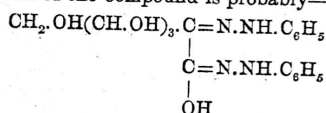
<sup>2</sup> Zeitschrift für Biologie, Band xxvii., p. 222, 1890.

substances. Similar results, when made to coincide, have been placed by Seliwanow's method by red-fermentation, using a method aimed at that, and that were due to modification of acid and carbonate, and carrying out the lævulose the but with reaction the extract

with water, alcohol, and ether, and dried. The calcium content of the salt prepared in this way was determined in 6 cases with the following results: (i.) 9.4 per cent., (ii.) 9.5 per cent., (iii.) 9.2 per cent., (iv.) 9.3 per cent., (v.) 9.4 per cent., and (vi.) 9.6 per cent., an average of 9.4 per cent., which corresponds closely to the theoretical calcium content, 9.39 per cent., of a salt with the formula  $(C_6H_5O_7)_2 Ca$ .

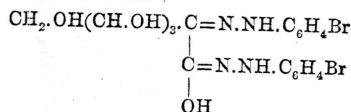
To separate the free acid from the calcium salt it was suspended in water and a stream of carbon dioxide gas passed through for two hours. The calcium carbonate precipitate was then filtered off, and the filtrate concentrated by evaporation *in vacuo* over sulphuric acid. A thick, yellowish, hygroscopic syrup, from which no crystals separated, even after several months, was obtained. It had a sweetish acid taste, was lævorotatory, fermented with brewer's yeast, rapidly reduced alkaline solutions of copper and bismuth, and gave both Seliwanow's and Pinow's tests.

The phenyllosazone and parabromphenyllosazone were then prepared by the method of Maquenne, and the melting point determined on the "bloc Maquenne." The phenyllosazone separated out as rather coarse yellow crystals arranged in sheaves. The purified product in all the cases examined had a melting point of 223°C., which is 7° lower than the melting point of dextrosazone and lævulosazone. The percentage of nitrogen in the osazone was determined in two cases by Dumas's method, giving in one instance 14.80 per cent. and in the other 14.99 per cent. These results suggest that the formula of the compound is probably—



—with a theoretical yield of 14.97 per cent. of nitrogen.

The parabromphenyllosazone was obtained as fine yellow felted needle-like crystals. In 4 cases of simple "lævulosuria" it was found to have the following melting points: (i.) 196°C., (ii.) 197°, (iii.) 197°, and (iv.) 198°. While in 5 cases in which the substance had been isolated from the urine of diabetics in which dextrose was also present the following results were obtained: (i.) 198°C., (ii.) 197°, (iii.) 198°, (iv.) 198°, and (v.) 196°. The close correspondence of the melting points in diabetic and non-diabetic cases suggests that the lævorotatory substance is the same in both. The percentage of nitrogen present in the parabromphenyllosazone was determined in two of the cases, one yielding 10.56 per cent. and the other 10.40 per cent., results which correspond to the theoretical yield of 10.52 per cent. for an osazone with the formula—

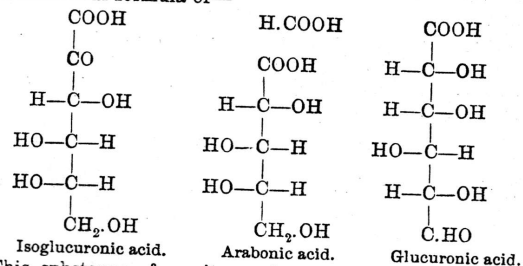


It will thus be seen that the melting point and nitrogen content of the phenyllosazone and parabromphenyllosazone do not correspond to the osazones formed by true lævulose, but that they point to the lævorotatory substance which occurs in the urine, both in diabetic and non-diabetic cases, being a ketonic acid. To confirm this a study of its oxidation products was undertaken.

10 c.c. of the syrup prepared in the manner previously described were dissolved in 100 c.c. of water and heated with 20 grm. of lead peroxide and 10 grm. of sulphuric acid on a water bath for three hours. The mixture was then cooled and filtered. The filtrate was treated with barium carbonate until the acid was neutralised, then boiled and filtered. The filtrate was shaken with animal charcoal, filtered, concentrated to 50 c.c., and mixed with 100 c.c. of absolute alcohol. After standing for four hours the mixture was filtered. The precipitate was then washed with absolute alcohol, dried, and the barium content determined. 0.7428 grm. was found to give 0.3718 grm. of barium sulphate, corresponding to 29.46 per cent. of barium for the original compound. This yield corresponds, within the limit of experimental error, to the theoretical yield of 29.40 per cent. of barium for barium arabonate,  $Ba(C_6H_5O_7)_2$ , the

oxidation product produced by the action of lead peroxide on an acid of the formula,  $CH_2.OH.(CH.OH)_3.CO.CO.OH$ .

To confirm the presence of arabonic acid a portion of the salt was dissolved in water and the barium precipitated by carbon dioxide gas, the excess of which was subsequently removed by boiling. After filtering off the precipitate of barium carbonate, the solution was evaporated *in vacuo* over sulphuric acid. In five days white crystals appeared, and these were found to have a melting point of 97°C. corresponding to that of arabonolactone. These results pointed to a structural formula of—



This substance, from its analogy to glucuronic acid, we propose to name isoglucuronic acid.

In the course of our investigations we have examined specimens of urine from 30 cases of so-called lævulosuria and 50 of diabetes, in which a lævorotatory substance was present along with the dextrose, but in none of them could any true lævulose be found, the lævorotatory body in each instance being proved to be isoglucuronic acid. The data upon which a diagnosis of lævulosuria has been based in most of the published cases are such that the results obtained might equally well be explained by the presence of isoglucuronic acid, for the reduction of Fehling's solution, a positive Seliwanow's reaction, lævorotation, these properties being abolished by previous fermentation with yeast, and the formation with phenylhydrazine of an osazone which has the melting point of glucosazone are characters shared by both bodies.

In some of the more recent cases reliance has been placed upon the formation of a crystalline calcium compound and the separation of a methylphenylhydrazine derivative with a melting point of 153°C.; but, as we have shown, isoglucuronic acid forms an insoluble compound with calcium, and we have found that with methylphenylhydrazine it yields an osazone which melts at 150°C. The difference between the two melting points is so slight that it cannot be relied upon as a means of differentiating the substances, especially as we have found that the melting point of methylphenyllævulosazone is not very sharp and is consequently difficult to determine with certainty. That this is the case is also suggested by the fact that melting points of 153°C.,<sup>2</sup> 159°C.,<sup>3</sup> and 158°–160°C.<sup>4</sup> for the compound are given in recognised text-books. In support of our contention that isoglucuronic acid and lævulose are distinct substances, it may be mentioned further that a mixture of equal parts of the methylphenyllosazones prepared under identical conditions has been found to melt at 120–130°C. on the "bloc Maquenne," whereas the osazone of lævulose melts at 162°C. and that of isoglucuronic acid at 155°C. The only published case in which it seems to have been conclusively proved that lævulose was present in the urine is that described by Otto Neubauer,<sup>5</sup> for in this instance the sugar was isolated in a crystalline

<sup>2</sup> Friedmann and Kempu: Abderhalden's Handbuch der Biochemischen Arbeitsmethoden, 1910, vol. iv., p. 1437.

<sup>3</sup> Pincussohn: Med.-Chem. Lab.-Hilfsbuch, 1912, p. 359.

<sup>4</sup> Neuberg and Strauss: Quoted by Schulz, Neubauer-Huppert, Analyse des Harns, 1910, p. 443.

<sup>5</sup> Münchener Medizinische Wochenschrift, 1906, Band lli., 1525.